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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/087,898	03/01/2002	Alexander Olek	81658A	4523
23685 7590 02/06/2007 KRIEGSMAN & KRIEGSMAN 30 TURNPIKE ROAD, SUITE 9 SOUTHBOROUGH, MA 01772			EXAMINER DEJONG, ERIC S	
			ART UNIT	PAPER NUMBER
			1631	
SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
3 MONTHS		02/06/2007	PAPER	

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/087,898

Applicant(s)

OLEK ET AL.

Examiner

Eric S. DeJong

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 November 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-31 and 35-44 is/are pending in the application.
- 4a) Of the above claim(s) 35-42 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-31, 43, and 44 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED OFFICE ACTION

Claim Objections

The objection of claim 14 because of minor informalities is withdrawn in view of amendments made to the instant claim.

Claim Rejections - 35 USC § 112

The previous rejection of claims 1-31, 43, and 44 under 35 U.S.C. § 112, second paragraph, as being indefinite is withdrawn in view of amendments made to the instant claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-31, 43, and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 43 each recite the limitation "concluding from the said knowledge base on the biological effect and/or activity of said at least one drug and/or pharmaceutical composition of said biological sample A from step (a)" (see for example, lines 16-18 of claim 1 and lines 19-21 of claim 43). This limitation causes the metes and bounds of the claim to be indefinite because the recited limitation is ambiguous as to what is actually concluded from "the said knowledge base on the biological effect and/or

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activity of said at least one drug and/or pharmaceutical composition of said biological sample A from step (a)." Claims 2-31 and 44 are also included under this rejection due to their dependence from either claim 1 or 43.

For the purpose of continuing examination, the limitation "concluding from the said knowledge base on the biological effect and/or activity of said at least one drug and/or pharmaceutical composition of said biological sample A from step (a)" has been construed to read on concluding from said knowledge base a biological effect and/or activity that said at least one drug and/or pharmaceutical composition has one said biological sample A in step (a) of the claimed process.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-31, 43, and 44 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-31, 43, and 44 are drawn to a process for determining the biological effect and/or activity of at least one drug and/or pharmaceutical composition. The claimed process comprises the abstract steps of analyzing cytokine methylation at chosen DNA site, selecting differentially methylated sites in said chosen DNA sites to generate a knowledge base, and concluding from said knowledge base the biological effect and/or activity of said at least one drug and/or pharmaceutical composition and, therefore, involves the application of a judicial exception. Regarding inventions involving the

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application of a judicial exception, said application must be a practical application of the judicial exception that includes either a step of a physical transformation, or produces a useful, concrete, and tangible result (State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998), AT&T Corp. v. Excel Communications Inc. (CAFC 50 USPQ2d 1447 (1999))). In the instant claims, there is no step of physical transformation that results from said application of judicial exception, thus the Examiner must determine if said application of a judicial exception produces a useful, concrete, and tangible result.

In determining if the application of a judicial exception produces a useful, concrete, and tangible result, the Examiner must determine each standard individually. For a result to be "useful," the application of a judicial exception must produce a result that is specific, and substantial. For a result to be "concrete," the application of a judicial exception must have a result that is reproducible. For a result to be "tangible," the application of a judicial exception must produce a real world result . Furthermore, the claim must be limited only to statutory embodiments.

Claims 1-31, 43, and 44 do not produce a tangible result. A tangible result requires that the claim must set forth a practical application of a judicial exception to produce a real-world result. This rejection could be overcome by amendment of the claims to recite that a result of the application of a judicial exception is outputted to a display, a user, a readily accessible memory or other computer on a network, or by including a physical transformation.

Claim Rejections – 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-11, 13-21, 23-26, 28, 31, 43, and 44 are rejected under 35 U.S.C. 102(e)(2) as being anticipated by Laird et al. (P/N 6,331,393 B1) in light of Klippel et al. (P/N 3,558,768).

The instant claims are drawn to methods for determining the biological effect and/or activity of at least one drug, chemical substance, and/or pharmaceutical composition comprising the steps of obtaining a biological sample A containing DNA, wherein said sample A was exposed to said at least one drug, chemical substance, and/or pharmaceutical composition, obtaining a biological sample B containing DNA, wherein said sample B was not exposed to said at least one drug, chemical substance, and/or pharmaceutical composition, subsequently analyzing the level of cytosine methylation at chosen sites of the DNA contained in samples A and B, selecting sites which are differentially methylated between the DNA in said samples to generate a knowledge base, and concluding the biological effect of said at least one drug, chemical substance, and/or pharmaceutical composition from said knowledge base.

Laird et al. disclose a method for determining methylation patterns (biological effect or activity) in genomic DNA (containing genes) after being treated with sodium bisulfite (sample A) (at least one drug and/or pharmaceutical composition) (see Laird et al., abstract), as stated in instant claims 1, 9, and 13. Klippel et al. is further relied upon in the instant rejection to demonstrate the use of sodium bisulfite in pharmaceutical compositions (see Klippel et al. col. 3, line 30 through col. 4, line 36). Laird et al. disclose methylation amounts in multiple samples are quantitatively determined based on reference to a control reaction (sample B) (see Laird et al., col. 5, lines 61-64) which represents an unexposed sample and analyzing methylation levels in samples A and B, as recited in instant claims 1 and 43. Laird et al. disclose using probes and primers to distinguish between methylated and unmethylated nucleic acid, amplifying the DNA, and detecting methylated DNA via fluorescence-based quantitative PCR (see Laird et al., col. 5, lines 16-64) which represents selecting sites differentially methylated. Figures 7 and 8 display data that represent a knowledge base generated based on the conclusive effect of sodium bisulfite treatment, as recited in instant claims 1 and 43. The gene names (i.e. ESR1 or MyoD1) in Figures 7 and 8 represent additional information used for the conclusion data found in these figures (i.e. correlation between MLH1 gene expression, MSI status, and promoter methylation status of MLH1 in Figure 8, col. 24, lines 30-31), as stated in instant claim 24. The x-axes in the 2 graphs of represent at least two individual rows of analyses, as stated in instant claims 17 and 25. This data presentation also shows all or a part of the sites used for the conclusion, as stated in instant claim 23. Further conclusions are drawn by Laird et al. (see Laird et

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al., col. 24, lines 48-67). Laird et al. disclose in higher order eukaryotic organisms, DNA is methylated only at cytosines located 5' to guanosine in the CpG dinucleotide (see Laird et al., col. 1, lines 14-17) which represents cytosine methylation. Laird et al. disclose contacting a DNA sample from a patient with a modifying agent, bisulfite (see Laird et al., col. 5, lines 19-20 and 31), as recited in claim 44. Laird et al. disclose various methods to identify altered methylation sites in cancer cells (see Laird et al., col. 3, lines 3-5) and determining DNA methylation patterns at specific loci (see Laird et al., col. 4, lines 12-15) which represents only one set of selected sites, as stated in instant claim 18. Laird et al. disclose selecting genes (see Laird et al., col. 19, line 5) which represents a knowledge base of different classes, as stated in instant claim 19. Laird et al. disclose using PCR, sequencing, fluorescent labeling (see Laird et al., col. 7, lines 26-65), as stated in instant claim 9. Laird et al. disclose using human colorectal adenocarcinoma (cancer) and normal mucosa (healthy) tissue samples (see Laird et al., Figures 7 and 8; col. 22, lines 46-49), as stated in instant claims 4 and 5. Laird et al. disclose 25 match-paired normal and tumor samples with MLH1 expression level and MLH promoter methylation as well as MYOD1 control gene (see Laird et al., Figure 8 and col. 8, line 64 to col. 9, line 12) which represent at least two methylation sites selected and analyzed in parallel, as stated in instant claims 11 and 21. Laird et al. disclose using parallel reactions with methylated, unmethylated, and control oligos of bisulfite-treated DNA samples (see Laird et al., col. 18, lines 36-39). Laird et al. disclose analyzing methylation status of the ESR1 locus in DNA samples which is a gene that contains hypermethylatable CpG islands that undergo de novo methylation in

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human colorectal tissue in all normal and tumor samples (see Laird et al., col. 18, line 67 to col. 19, line 17 and col. 22, lines 29-30) which represents methylation sites that are located in methylation relevant genes associated with cancer, as stated in instant claim 14. Laird et al. disclose using PCR primers and probes used for sequences representing fully methylated and fully unmethylated DNA in several genes, including ESR1 (col. 19, lines 32-40), which represents analyzing all potential methylation sites of the DNA, as stated in instant claim 10. Laird et al. disclose isolating DNA via proteinase K digestion from sperm and HCT116 (human colorectal cell line), treated with sodium bisulfite, and then the DNA samples are analyzed by COBRA analysis or amplification process using fluorescence-based real-time quantitative PCR (see Laird et al., col. 16, line 55 to col. 17, line 17), as stated in instant claims 6-8. Laird et al. disclose that altered DNA methylation pattern of cytosine residues is mutagenic (see Laird et al., col. 2, lines 34-36) which demonstrates that the colorectal samples mentioned above represent genes associated with ulcerative colitis which is a type of colon disease, as stated in instant claim 15. In Example 4, Laird et al. disclose analyzing the methylation DNA samples from the same patient (see Laird et al., col. 22, lines 29-32) which represents analyzing methylation sites that are personalized, as stated in instant claims 16 and 28. In Example 5, Laird et al. disclose using 25 patients with tumor and normal tissue samples surgically removed (dissected tissue immediately frozen) (see Laird et al., col. 23, lines 28-37) which represents histologically, dissected biological material from healthy and diseased individuals in instant claims 2-4. Laird et al. disclose the use of paraffin embedded samples (see Laird et al., col. 9, lines 42-46). Laird et al. disclose

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using the TaqMan, Lightcycler, Sunrise technologies, as well as ABI Prism 7700 Sequence Detection System (see Laird et al., col. 14, lines 5-20) which represent selection at least partially performed automatically by an automate or computer device and conclusions performed by a computer system, as recited in instant claims 20, 26, and 31.

Response to Arguments

Applicant's arguments filed 11/08/2006 have been fully considered but they are not persuasive.

In regards to the rejection of claims as being anticipated by Laird et al., applicants argue that the instant claims have been amended to recite "at least one drug and/or pharmaceutical composition" and as such, the claims no longer read on sodium bisulfite. Applicants further argue that sodium bisulfite is neither a drug nor a pharmaceutical composition as evident from the fact that sodium bisulfite has no known therapeutic use.

In response, it is first noted that neither the instant claims nor the instant specification provides a definition for the terms "drug" or "pharmaceutical composition" that limit said claims to only encompassing chemical substances that have a known therapeutic use. Further, the instant rejection relies upon Klippel et al. to demonstrate the use of sodium bisulfite as an ingredient in pharmaceutical compositions (see Klippel et al. col. 3, line 30 through col. 4, line 36).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. DeJong whose telephone number is (571) 272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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John S. Brusca / February 2006
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PRIMARY EXAMINER